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Progress Report

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## Introduction

The current mode of therapeutic administration is not efficient as it lacks targeting, specificity, and control over bioavailability. These shortcomings lead to the need for frequent injections, patient compliance issues, and, sometimes, severe side effects and drug resistance.<sup>1, 2</sup> On the other hand, drug delivery carriers can initially protect the therapeutics, circulate in the blood stream, and deliver the therapeutic only to the target site and with the desired rate, thereby increasing the efficacy of the system.<sup>2-4</sup> Initial drug delivery formulations have been tested in clinical trials and some have become pharmaceutical products.<sup>5, 6</sup> However, while these carriers are able to contain the therapeutics and release them over a prolonged period as compared to free-drug infusions, they still need major improvements to become the ideal candidates for drug delivery, such as active targeting, prolonged circulation, and specific release kinetics.<sup>7</sup> Another issue faced by these carrier systems is cellular drug resistance. This may be overcome by the incorporation of multiple therapeutics in a single carrier system, with specific release profiles to address differences in pharmacological windows of each therapeutic.<sup>8-10</sup> Ideally, these carrier systems would take advantage of possible synergistic effects between the therapeutics to increase the effectiveness of the combination therapy.<sup>11, 12</sup> In order to make such complex carrier systems several approaches have been proposed, many of which use stimuli responsive material (sensitive to pH, temperature, light, and/or oxidative stress) to create on-demand and complex release profiles that can be tuned based on the needs of incorporated therapeutics.<sup>7, 13-17</sup>

Multiple fabrication techniques exist for the incorporation of such stimuli responsive material in carrier systems, however, only a few exist that are capable of spatioselectively incorporating multiple therapeutics in separate environments and providing distinct release profile for each.<sup>18</sup> Generally, current carrier system with multiple therapeutics do so in an isotropic environment and may suffer from antagonistic interactions between the drugs.<sup>18-21</sup> The few systems capable of encapsulating each therapeutic in a unique environment within a single particle include: capsules,<sup>16</sup> LbL (Layer-by-Layer) particles,<sup>22, 23</sup> templated particles,<sup>24, 25</sup> core-shell structures,<sup>26, 27</sup> and dendrimers.<sup>28, 29</sup> To date, very few of these strategies have led to particles with distinct release profiles of multiple drugs from the same carrier system.<sup>30</sup>

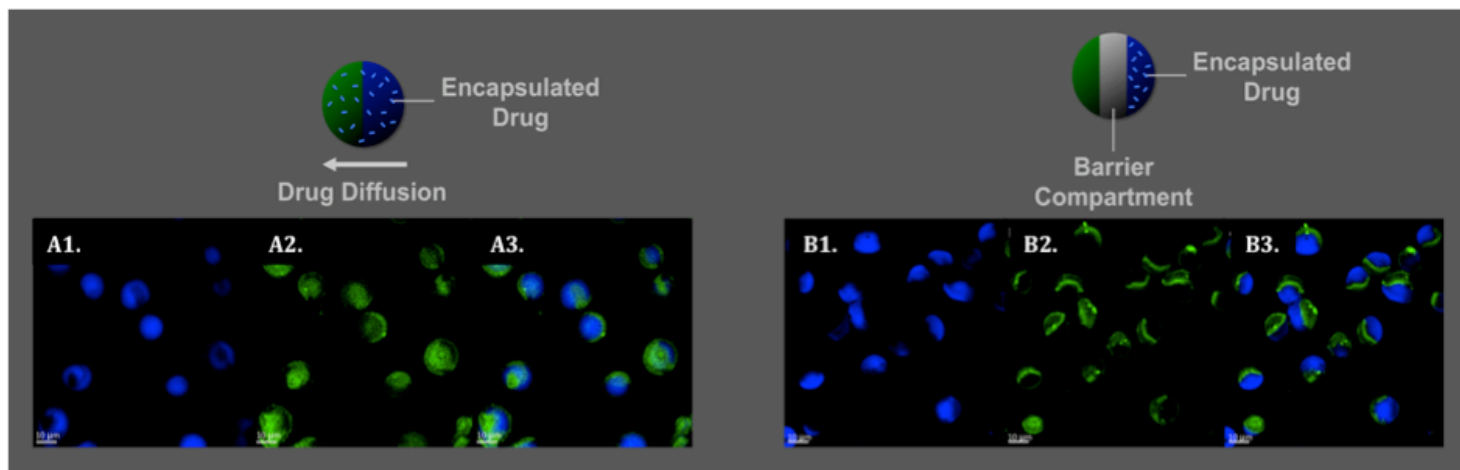
As an alternative, electrohydrodynamic (EHD) co-jetting<sup>31</sup> can be used to fabricate anisotropic particles with distinct internal geometries that can be used to encapsulate different therapeutics and polymer combinations for distinct release kinetics of each incorporated drug.<sup>31-36</sup> So far, we have shown the fabrication of particles and fibers with multiple compartments,<sup>34, 37, 38</sup> and, more recently, the incorporation of a variety of different polymers, such as hydrogels (e.g., poly (ethylenimine) and poly (ethylene oxide),<sup>39, 40</sup> polysaccharides (dextran),<sup>41</sup> or poly(acrylamide-co-acrylic acid),<sup>42</sup> poly(methyl methacrylate),<sup>40</sup> poly(styrene),<sup>40</sup> and poly(vinyl cinnamate)<sup>40, 43, 44</sup> in separate compartments. This method can be used to fabricate multicompartmental nanocarriers containing multiple cancer therapeutics with distinct release profiles that are targeted to specific sites in the body.<sup>31</sup>

The EHD process is a reproducible, reliable, versatile, and efficient method to create multifunctional nano- and micro-particles. In the EHD process, multiple polymer solutions are flown in a laminar regime through syringes tipped with metal needles. The needles are connected to a high voltage source, which is grounded via a metal collector placed beneath the syringes. As a DC voltage is applied to the needles, the solutions at their tip form into a Taylor cone.<sup>45</sup> At the end of this Taylor cone, a thin, high-speed jet is formed that travels toward the grounded electrode.<sup>34</sup> The jet exiting the tip of the Taylor cone becomes thinner and eventually breaks into small droplets. During this process, the solvents evaporate rapidly, leaving behind solid anisotropic particles that are collected on a counter electrode. Due to the rapid evaporation of the solvents and the laminar flow regime used, the polymers do not have sufficient time to mix, and, thus, result in particles with distinct compartments. In these

particles, the number of compartments is determined based on the number of individual needles originally used.<sup>32, 34</sup>

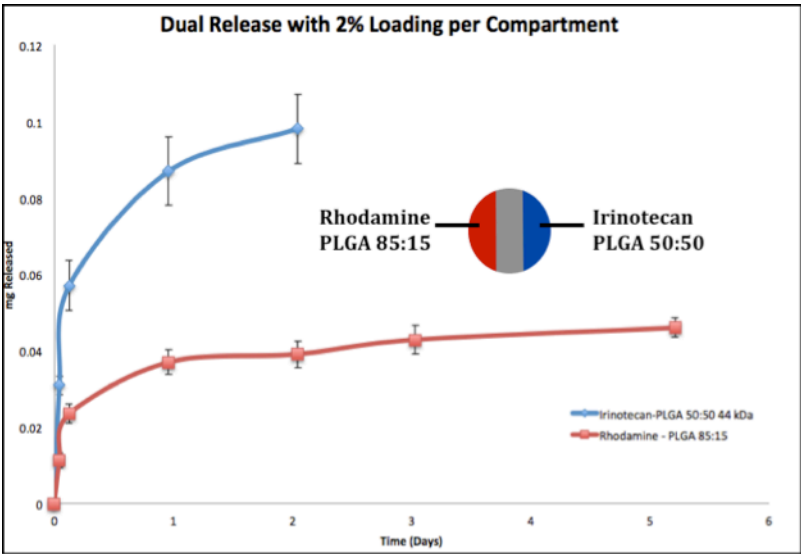
## Progress Report of Research Tasks.

As part of Aim 1, particles with various polymers in each compartment were fabricated. For dual release of therapeutics with distinct profiles, particles containing two polymers with varying degradation rates were synthesized. To do this, one side contained a PLGA (poly (lactide-co-glycolide)) with a higher molecular weight and ratio of lactide to glycolide (50-75 kDa and 85:15), than the second compartment (44 kDa and 50:50). The higher molecular weight and ratio of lactide to glycolide causes the first polymer to degrade more slowly than its counterpart, thereby releasing its payload at a slower rate. Low molecular weight molecules, such as dyes and therapeutics, can be incorporated into multicompartmental particles by adding them to the polymer solutions used for jetting. However, unlike the polymers that are high molecular weight (on the orders of tens of kDa) and do not have sufficient time to mix during the jetting, the low molecular weight molecules (less than a kDa) can diffuse and mix with the other jetting solutions much faster. While this is not an issue when the molecules are used at low concentrations (less than 5% w/w of the polymer content), it can become a major problem when a high loading of a therapeutic is used. In order to combat this problem, triphasic particles were fabricated with a middle compartment that could act as a 'barrier'. This 'barrier compartment' is composed of relatively hydrophobic, high molecular weight polymers that act as a deterrent to the diffusion of molecules to the other compartments. While the low molecular weight dyes/therapeutics have sufficient time to mix into the other compartment in bicompartmental systems (**Figure 1.A**), they do not have enough time to diffuse through triphasic particles with this 'barrier compartment', and thus stay compartmentalized (**Figure 1.B**). We were able to show compartmentalization of a cancer therapeutic, Irinotecan, up to a high loading of 25% w/w of the polymer in one compartment.



Nanoparticles containing two different low molecular weight entities in separate compartments were fabricated using the barrier compartment method and tested via release studies. As part of Aim 3, particles incorporating a cancer therapeutic, Irinotecan, in one compartment, and a low molecular weight dye, Rhodamine, in the other were fabricated. These particles were approximately 800 nm in size and the encapsulation of the molecules was observed via CLSM (Confocal Laser Scanning Microscopy) imaging. In this case, Irinotecan autofluoresces in the blue channel while Rhodamine in the red

**Figure 1:** High loading of therapeutics can be compared without a barrier compartment, the drug (blue) diffuses through the barrier compartment, the drug is encapsulated only in one

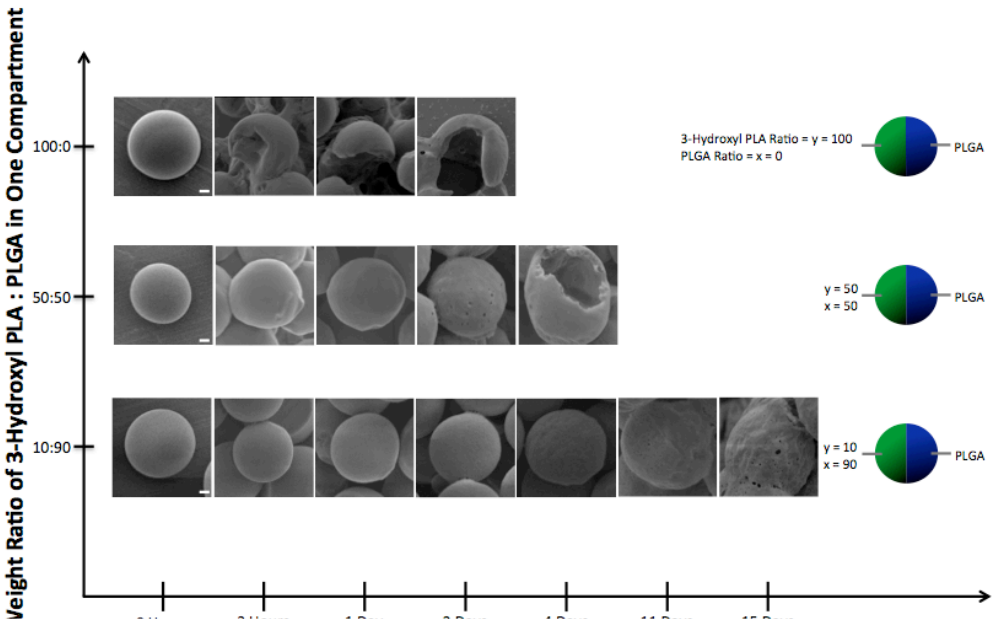


**Figure 2:** Dual distinct release from multi-compartmental particles with a barrier compartment. A low molecular weight dye (Rhodamine-Red) is encapsulated in one compartment and a low molecular weight drug (Irinotecan-Blue) in the other.

channel. Once the presence of the molecules were confirmed release studies with the particles were done to show distinct release of the two molecules (**Figure 2**). Here the difference in release profiles were achieved based on the molecular weight of the polymers used (44 kDa for Irinotecan and 50-75 kDa for Rhodamine) and the lactide-to-glycolide ratio of the polymers (50:50 for Irinotecan and 85:15 for Rhodamine), both of which determine the rate of the degradation of the polymer. As a result, the compartment with the lower molecular weight and higher ratio of glycolide released its therapeutic load (Irinotecan) first.

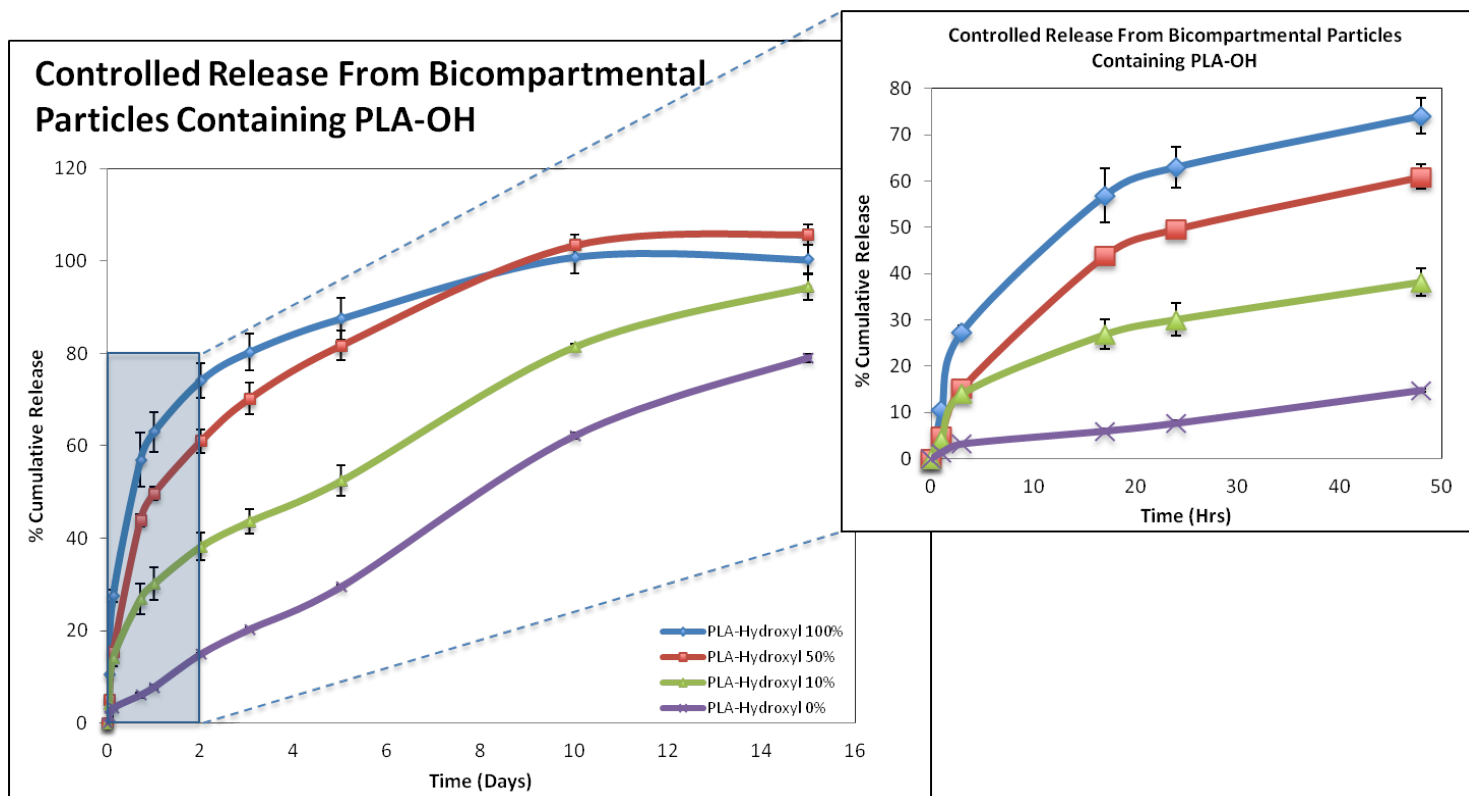
To further explore the effect on the release profiles of therapeutics, different polymer, or different ratios of the same polymers, can be explored to accurately tune-in release kinetics. A hydroxyl-modified polylactide (3-Hydroxyl PLA) has been synthesized in the Lahann laboratory with a fast degradation period of several hours. Particles with this polymer were fabricated and structurally characterized based on the guidelines established in Aim 1. Particles with PLGA in one compartment

and different percentages of 3-Hydroxyl PLA (0, 10, 50, or 100%) in the other compartment were fabricated, and their degradation was characterized via SEM (Scanning Electron Microscopy) imaging (**Figure 3**). Based on these results, it was confirmed that selective degradation of one side could be achieved and rate of the degradation could be controlled. Going forward, particles loaded with



**Figure 3:** Selective degradation of particles with different ratios of 3-Hydroxyl PLA in one side as a function of time

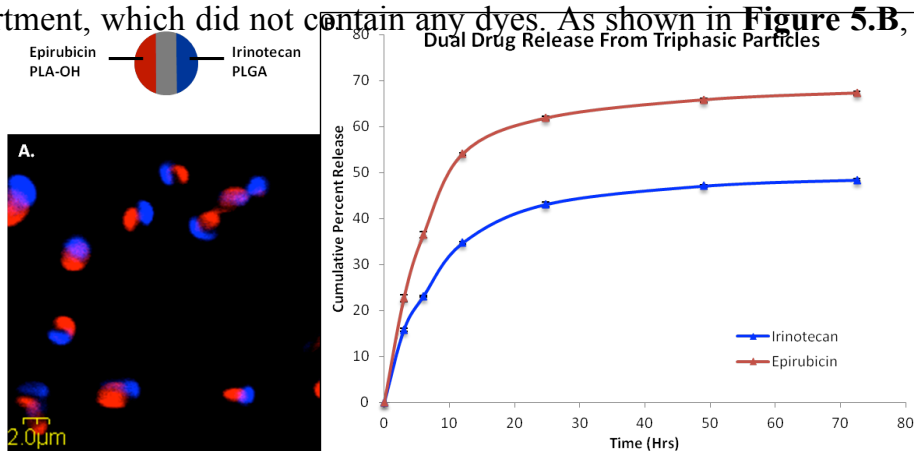
Irinotecan were fabricated to show the controlled release of therapeutics from these particles. Depending on the amount of 3-Hydroxyl PLA used, the release profile of the encapsulated therapeutic, could be tuned-in: as the level of 3-Hydroxyl PLA increased, so did the release rate of Irinotecan (**Figure 4**).



**Figure 3:** Release of therapeutics can be tuned-in by altering the composition of each compartment. Here, bicompartamental particles with PLGA on one side and different ratios 3-Hydroxyl PLA on the other side were used for release studies. As the ratio of 3-Hydroxyl PLA was increased (from zero to 100%), the release of the therapeutic was enhanced.

Triphasic particles combining these two methods (barrier compartment and use of rapidly degrading polymers) were fabricated. In this case, two cancer therapeutics, Epirubicin and Irinotecan, were contained in separate sides and released from particles (**Figure 5**). Both Epirubicin and Irinotecan autofluoresce (red and blue, respectively) and CLSM was used to show that the drugs stay compartmentalized (**Figure 5.A**). The empty space seen between the two compartments in some of the particles represents the barrier compartment, which did not contain any dyes. As shown in **Figure 5.B**, the release of the therapeutics from the particles is distinct and is expected based on previously shown data: Epirubicin contained in the 3-Hydroxyl PLA compartment is released faster than Irinotecan that is in the PLGA compartment.

To more accurately control the release of therapeutics from particles, materials with on-demand degradation/release characteristics can be used. A number of these

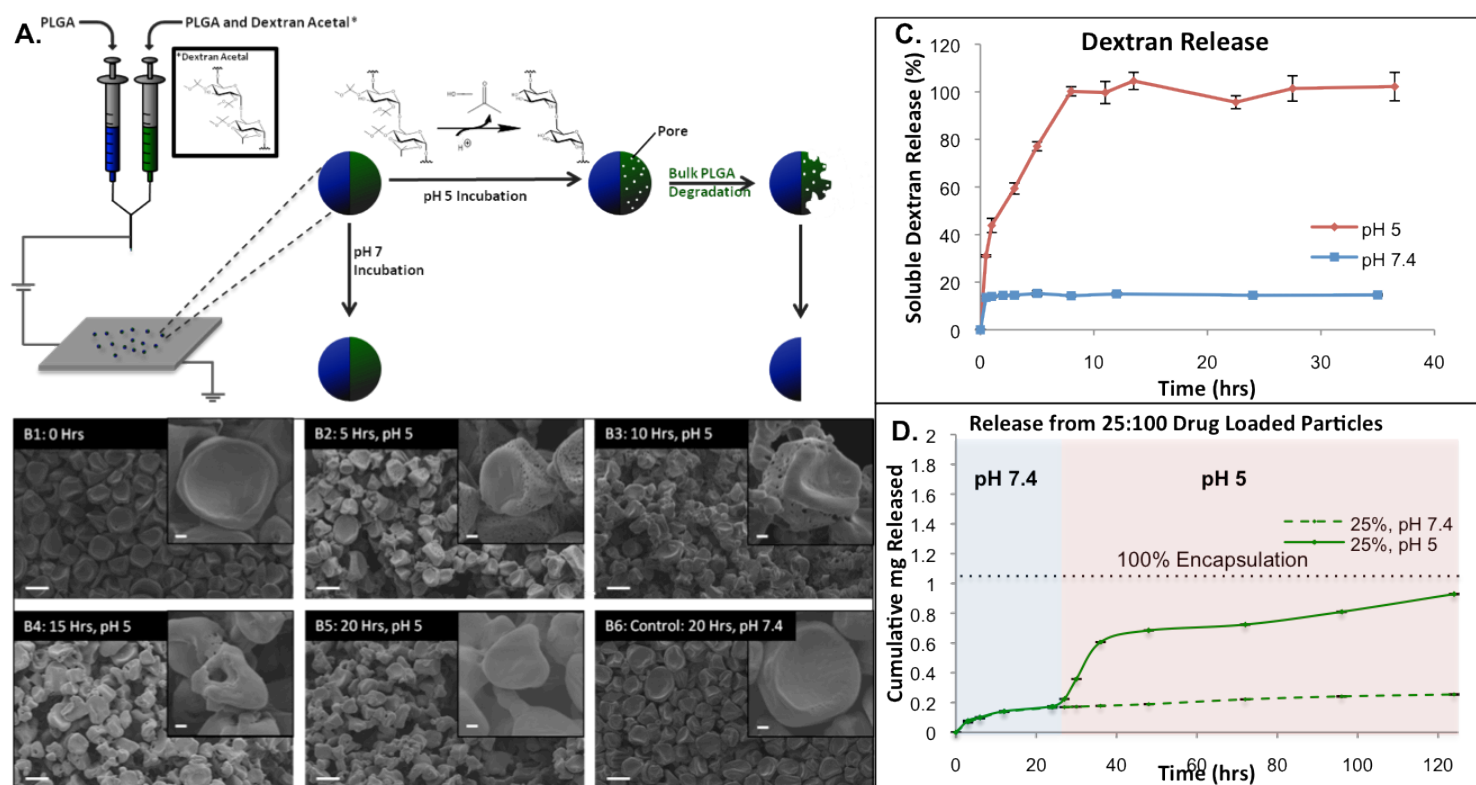


**Figure 5:** Dual release of cancer therapeutics from bicompartamental particles. Here, one side contains PLGA and Irinotecan and the other contains Epirubicin and 3-Hydroxyl PLA. A: Compartmentalized particles containing Epirubicin (autofluorescing red) and Irinotecan (autofluorescing blue) in separate compartments. The barrier compartment does not contain any dyes. B: Dual distinct release of cancer therapeutics from multinhasic particles



polymers have recently been used, and they are typically controlled via an external stimulus (pH, UV, IR, temperature, etc.).<sup>46</sup> Acetal dextran is one such example, as it is pH responsive.<sup>47</sup> At physiological pH, this polymer is stable and water insoluble, but at acidic pH the polymer becomes de-protected and water-soluble (**Figure 6.A**). Thus, particles made of such a polymer will stay intact in the blood stream and will only start to dissolve away and release their cargo in environments with an acidic pH (such as the endosome, the extracellular matrix surrounding tumors, and inflamed tissue). The use of such polymers in multicompartmental particles can result in on-demand degradation of one compartment and release of therapeutics.

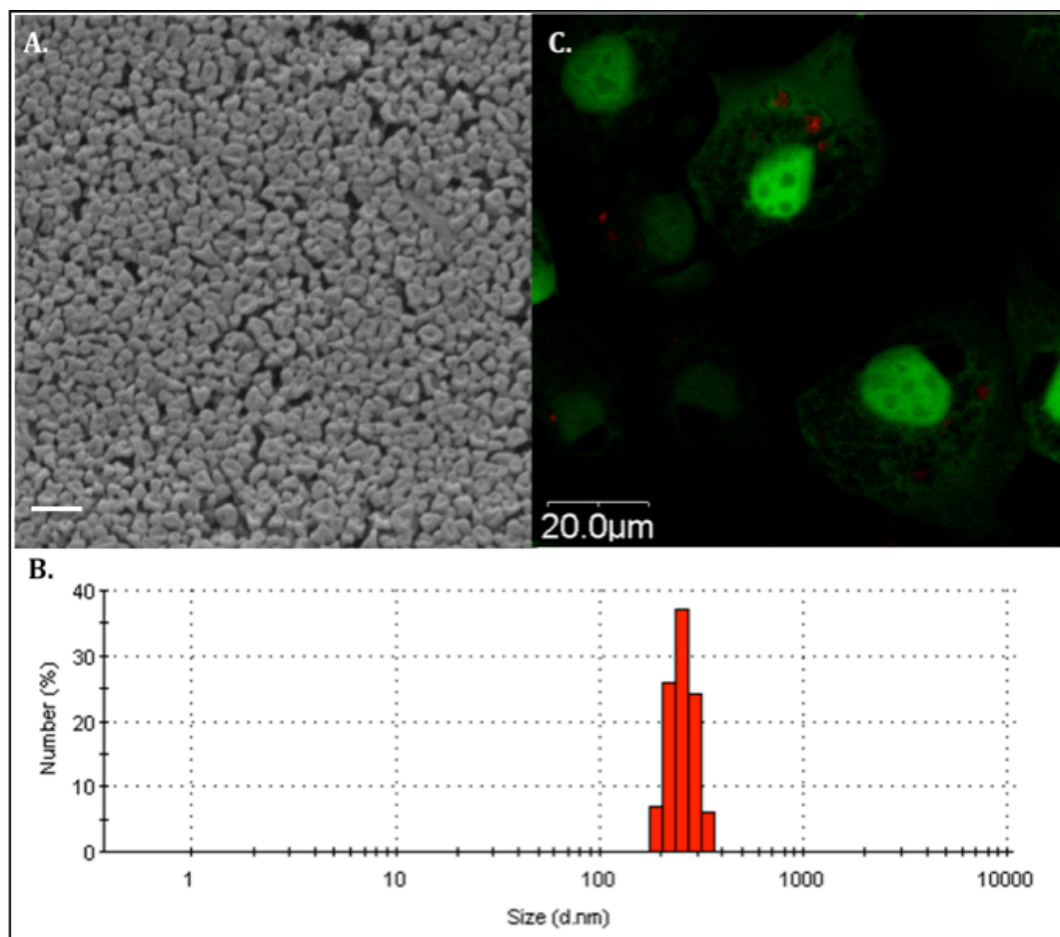
Particles with 75% w/w of acetal dextran in one compartment were synthesized and their degradation kinetics were followed via SEM, following the procedures outlined in Aim 1. It was shown that upon incubation at pH 5, the particles develop visible pores by 5 hrs (**Figure 5.B2**), and start to degrade and completely lose one side by 20 hrs (**Figure 5.B3-5**). In contrast, when incubated in physiological pH, the particles stay intact (control **Figure 5.B1** is similar to 20 hours incubation at pH 7.4 **Figure 5.B6**). In addition, the release of free dextran was quantified (**Figure 5.C**), which showed that the polymer is released from particles within a 10-hour period in pH 5 (agreeing with the SEM data). Next, particles containing dextran and Irinotecan in one compartment were fabricated and release studies were conducted (**Figure 5.D**). Two sets of particles (four replicas each) were incubated at pH 7.4 for 24 hours and their release kinetics were measured at predetermined intervals (3, 6, 12, and 24 hours). At the 24-hour mark, one set was switched to pH 5 (solid green line) while the other was kept at pH 7.4 (dotted line). While there was minimum release for the set kept at pH 7.4, there was a rapid release of Irinotecan from the set in pH 5 as the dextran was de-protected and released. A slower release of the Irinotecan follows this rapid release, which is due to the fraction of the drug encapsulated in the PLGA component of the compartment.



**Figure 5:** Morphology, degradation, and release from bicompartmental particles containing acetal dextran. A: Bicompartmental particles containing acetal dextran in one compartment are fabricated through the EHD co-jetting procedure. The particles are pH responsive. Upon incubation in pH 5, the acetal dextran is deprotected, released, and pores are created on one side of the particles that result in the enhanced degradation of one side. At physiological pH, the acetal dextran is not deprotected and the particles do not have any pores. B: SEM images showing a timed study of particle incubation at two different pHs. C: Release of soluble dextran from particles at two different pHs. D: Release of a therapeutic from the particles. Here the therapeutic is encapsulated in the acetal dextran containing side and is released once incubated in pH 5 (at the 24 hour mark).



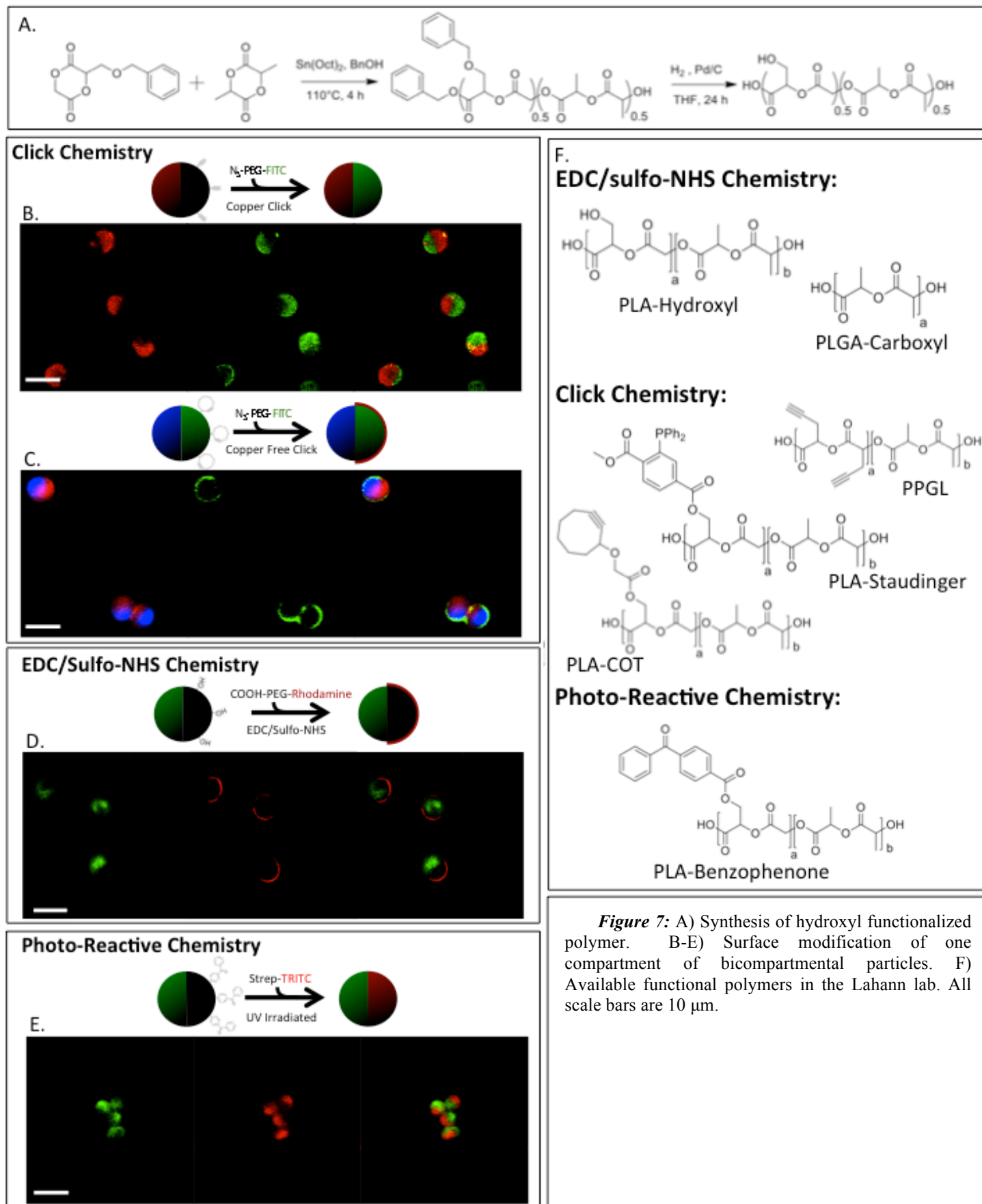
In order for such on-demand particles to be clinically applicable, they must be nano-sized and monodispersed. As part of Aim 1, various jetting parameters were changed to achieve nanoparticles, especially the polymers used, their molecular weight, their concentrations, the solvents used and any additives. For example, nanoparticles containing acetal dextran in one compartment were fabricated through the EHD co-jetting process by changing the solvents used during jetting. The particles were then separated into the relevant size ranges using serial centrifugation. As shown in **Figure 6.A-B**, the particles are monodispersed as seen in SEM and quantified by Dynamic Light Scattering (DLS). These particles were incubated with breast cancer cells and their cellular uptake was visualized. **Figure 6.C** shows the results of the uptake studies: here the cells autofluoresce green (they have been modified by a GFP marker) and the nanoparticles contain a red dye. Based on preliminary results, it appears that the particles are taken up through endocytosis. It can be projected that at this point due to the low acidic pH, such particles would release their cargo into the cellular environment.



**Figure 6:** Monodispersed Nanoparticles containing DA in one compartment and their cell uptake. A and B: SEM and DLS of bicompartmental particles with an average size of 200-300 nm. C: Cellular uptake of the Nanoparticles through endocytosis. Here, the nanoparticles contain a red dye and the breast cancer cell line autofluoresce green (GFP).

As shown in **Figure 6.A-B**, the particles are monodispersed as seen in SEM and quantified by Dynamic Light Scattering (DLS). These particles were incubated with breast cancer cells and their cellular uptake was visualized. **Figure 6.C** shows the results of the uptake studies: here the cells autofluoresce green (they have been modified by a GFP marker) and the nanoparticles contain a red dye. Based on preliminary results, it appears that the particles are taken up through endocytosis. It can be projected that at this point due to the low acidic pH, such particles would release their cargo into the cellular environment.

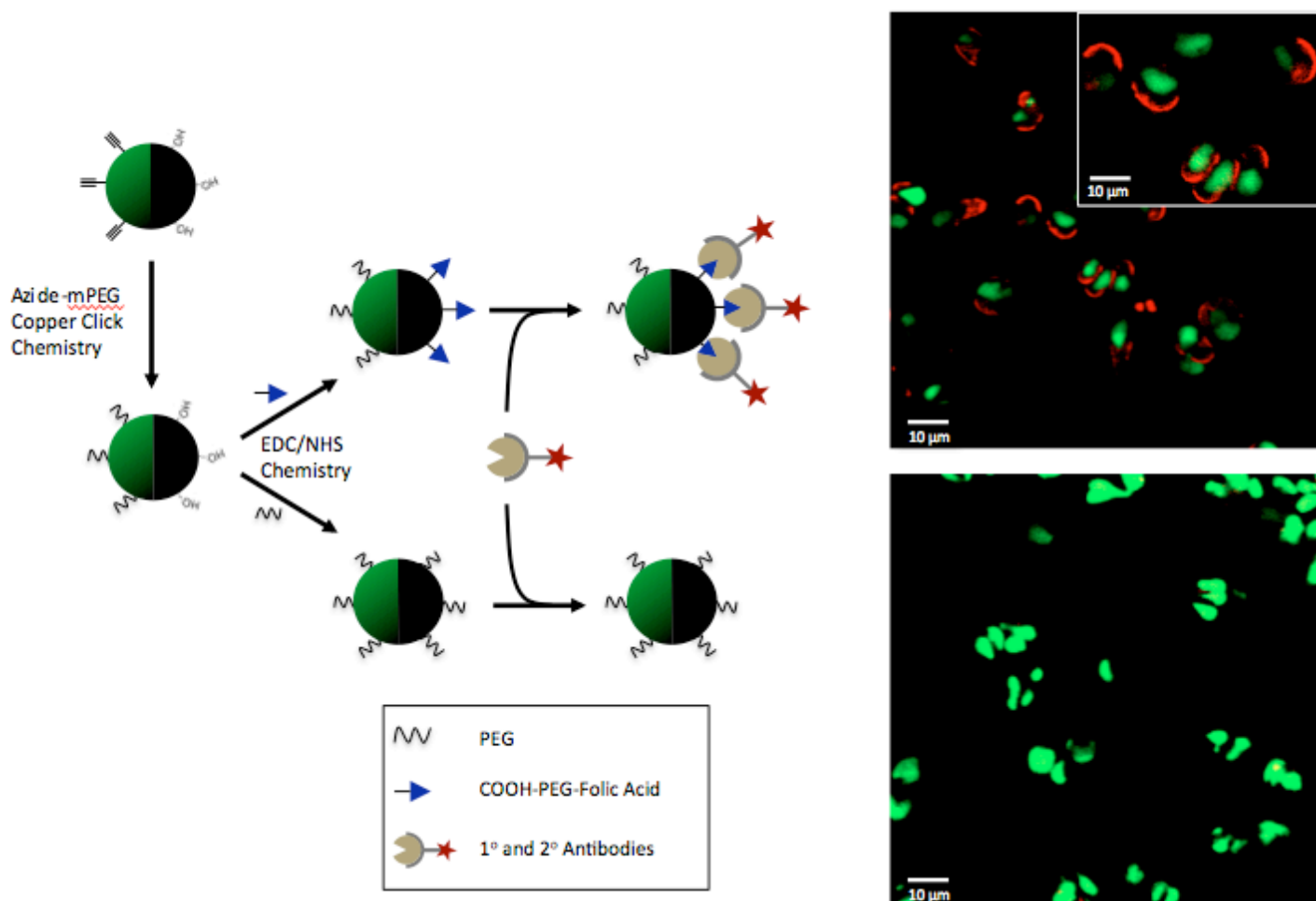
Once the design and synthesis of nanoparticles for co-administration of two different breast cancer drugs (Aim 1) and the preparation of the particles using optimal drug combinations and their respective controlled release studies (Aim 3) were accomplished, the surface modification of the particles was pursued for the attachment of targeting and stealth moieties. In the Lahann lab, functionalized polymers containing a variety of different and orthogonal chemical moieties have been synthesized. These polymers are PLA-based, and are thus both easily integrated into the jetting solutions and biodegradable. These polymers were each separately encapsulated in one side of a bi-compartmental particle, while the second side was composed entirely of PLGA, and was thus inert. The functional groups were then surface modified and, using fluorescent markers and CLSM imaging, the selective surface modification of each side was shown (**Figure 7**).



**Figure 7:** A) Synthesis of hydroxyl functionalized polymer. B-E) Surface modification of one compartment of bicompartamental particles. F) Available functional polymers in the Lahann lab. All scale bars are 10  $\mu\text{m}$ .

Once the selective surface modification of polymers using the functional polymers was established, the attachment of stealth (PEG: polyethylene glycol) and targeting (folic acid) moieties was explored. In

this case, the particles were first PEG-ylated through the use of click chemistry between the azide groups on the PEG chains and the acetyl groups of the polymer, followed by the attachment of the folic acid through EDC/Sulfo-NHS chemistry with the carboxyl group of the folic acid and the hydroxyl groups contained in the second compartment. The presence of the targeting molecule is then demonstrated through the use of an antibody specific to folic acid. The results and respective controls are shown in **Figure 8**, which demonstrates the effective surface functionalization of bicompartamental particles to selectively incorporate both stealth and targeting moieties.



**Figure 8:** Dual and selective surface functionalization of bicompartamental particles. One side of the particle, containing acetylene functionalized with PEG through click chemistry, while the second side is functionalized with folic acid through EDC/Sulfo-NHS chemistry. The folic acid is then labeled through antibody staining. The top, right image is of the functionalized particles with antibody staining, while the bottom image is of PEG-ylated control particles without folic acid.

In this report, we have outlined the progress of the research done in the Lahann lab towards accomplishing the Aims of this grant. Thus far, we have been able to meet the goals of both Aims, by fabricating bi- and tri-compartmental particles through the EHD co-jetting, encapsulating different polymers and therapeutics in each, demonstrating the optimal release profiles for various drug combinations, and optimizing the size and polydispersity of such particles. In addition to meeting these goals, we have furthered our study by incorporating functional polymers into these particles for the attachment of stealth and targeting moieties to enhance the efficacy of our nanoparticle system.

## Key Research Accomplishments.

- i. Identification and evaluation of suitable polymer combinations for multicompartmental carriers
- ii. Specific and independent degradation and release of bi- and tri-compartmental particles
- iii. Fabrication of particles with suitable size and polydispersity
- iv. Synthesis of functional polymers for selective surface modifications
- v. Selective surface modification of particles to include targeting and stealth moieties

## Reportable Outcomes.

M.D./Ph.D. student Asish Misra and Ph.D. student Sahar Rahmani have advanced to Ph.D. candidacy in Biomedical Engineering based on their work in this project.

The following publications have resulted based on the work done in this project:

1. T. H. Park, T. W. Eyster, J. M. Lumley, S. Hwang, K. J. Lee, A. C Misra, S. Rahmani, and J. Lahann, “Photoswitchable Particles for On-Demand Degradation and Triggered Release”, *Small*, **2013**, DOI: 10.1002/smll.201201921.
2. J. Lahann and S. Mitragotri, “Materials for Drug Delivery: Innovative Solutions to Address Complex Biological Hurdles”, *Advanced Materials*, **2012**, 24, 3717-3723.
3. A. C Misra, S. Bhaskar, N. Clay, and J. Lahann, “Multicompartmental Particles for Combined Imaging and siRNA Delivery”, *Advanced Materials*, **2012**, 24, 3850-3856.
4. S. Hwang and J. Lahann, “Differentially Degradable Janus Particles for Controlled Release Applications”, *Macromolecular Rapid Communications*, **2012**, 33, 1178–1183.
5. E. Sokolovskaya, J. Yoon, A. C. Misra, S. Bräse, J. Lahann, Controlled Microstructuring of Janus Particles Based on a Multifunctional Poly(ethylene glycol), *Macromolecular Rapid Communications*, **2013**, 34, (in press).

The following presentations have resulted based on the work done in this project:

1. S. Rahmani, S. Saha, T.-H. Park, J. Yoon, A. Dishman, K. Mahajan, V. Lai, and J. Lahann, “Multicompartmental Carriers for Theranostic Applications”, Material Research Society Fall Meeting, Boston, MA **2012**.
2. A. C Misra, S. Bhaskar, N. Clay, J. Yoon, S. Rahmani, and J. Lahann, “Multicompartmental Nanocarriers for Cancer Theranostics”, Material Research Society Fall Meeting, Boston, MA **2012**.
3. A. C Misra, T. H. Park, S. Bhaskar, N. Clay, J. Yoon, S. Rahmani, M. Ricci, R. P. Carney, T. M. Carney, F. Stellacci, and J. Lahann, “Multicompartmental Nanocarriers for Cancer Theranostics”, Engineering Graduate Symposium, University of Michigan, MI, **2012**.

4. S. Saha, S. Bhaskar, N. Clay\*, J. Lahann Controlled bending in bicompartamental microcylinders. 241st ACS National Meeting & Exposition, Anaheim, CA, United States, March 27-31, **2011**.
5. S. Rahmani, J. Yoon, A. C. Misra, J. Lahann, Biodegradable Multi-compartmental Particles for Sustained Drug Delivery of Chemotherapeutics, **2011** MRS Spring Meeting, San Francisco, CA.
6. T.-H. Park, A. Misra, D.W. Lim, T.W. Eyster, S. Hwang, S. Carney, F. Stellacci, J. Lahann, Polymer microparticles anisotropically functionalized with rippled gold nanoparticles for targeting of cell membranes. MRS Meeting, San Francisco, LA, United States, April **2011**.
7. T.-H. Park, J.M.\* Lumley, T.W. Eyster, S. Hwang, J. Lahann, On-demand degradation of acetal-modified dextran particles fabricated by electrospray, 242nd ACS National Meeting, Denver, CO, United States, August, **2011**.
8. K.J. Lee, S. Hwang, J. Yoon, T.-H. Park, J. Lahann, Spatially confined photoreactions in multicompartamental colloids and fibers prepared by electrohydrodynamic co-jetting, 242nd ACS National Meeting, Denver, CO, United States, August, **2011**.
9. K.J. Lee, J. Lahann Preparation of shape-switching colloids using electrohydrodynamic co-jetting, 242nd ACS National Meeting, Denver, CO, United States, August, **2011**.
10. J. Lahann, Multicompartamental Particles and Fibers for Biomedical Applications, Wyss Institute, Harvard University, Cambridge, MA, **2011**.
11. J. Lahann, Multicompartamental Particles and Fibers for Biology and Medicine, University of Bayreuth, Germany, **2011**.
12. J. Lahann, Three-dimensional Engineering of Multiphase Particles, Gordon Research Conference, **2011**.
13. J. Lahann, Micro- and Nanoparticles with Multiple Compartments, MRS Conference, San Francisco, CA, **2011**.
14. J. Lahann, Designer Colloids and Interfaces, General Motors, Warren, MI, **2011**.
15. J. Lahann, Multicompartamental Particles and Fibers, Columbia University, New York City, **2012**.
16. J. Lahann, Multicompartamental Particles and Fibers, University of Wisconsin Madison, WI, **2012**.
17. J. Lahann, Multicompartamental Particles and Fibers, *Small Symposium, Singapore*, **2012**.
18. J. Lahann, Multicompartamental Particles and Fibers, *Society of Biomaterials, New Orleans* **2012**.
19. J. Lahann, Multicompartamental Particles and Fibers, NanoGune San Sebastian, Spain, **2012**.
20. J. Lahann, Multicompartamental Particles and Fibers, Department of Polymer Chemistry, Karlsruhe Institute of Technology, Karlsruhe Germany, **2012**.
21. J. Lahann, Multicompartamental Particles and Fibers, University of Jena, Germany, **2013**.
22. J. Lahann, Multicompartamental Particles and Fibers, *University of Pennsylvania, Philadelphia* **2013**.

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